

Draft RoC Monograph on Haloacetic Acids Found as Water Disinfection By-Products

Studies in Experimental Animals



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July 24, 2017





Studies in Experimental Animals

Outline

Overview of studies in experimental animals

Study quality assessment

Cancer assessment

- Liver tumors
- Tumors at other sites
- Summary

Overview of Animal Studies

Six haloacetic acids had chronic cancer data available

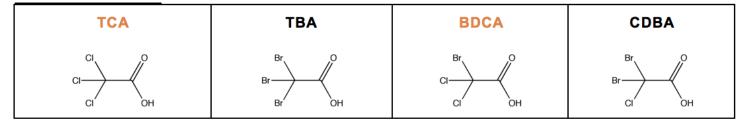
Mono-haloacetic acids

MCA	мва	MIA
CIOH	Br	ОН

Di-haloacetic acids

DCA	DBA	DIA
CI OH	Br OH	OH
BCA	CIA	BIA

Tri-haloacetic acids





Overview of Animal Studies

- 19 publications met inclusion criteria.
 - Reported on the presence or absence of neoplastic and related lesions.
 - Had a concurrent or historical control group.
 - Chronic studies with a duration of 12 months or greater or were studies with transgenic animals or co-carcinogen studies, e.g., initiation-promotion (i-p) studies.



Study Quality and Utility Assessment

Signaling Questions

Study design/population

Exposure conditions

Outcome assessment and measurement

Confounding

Analysis and reporting

Overall study utility:

High (+++)

Moderate (++)

Low (+)

Inadequate (0)

Responses for questions:

- Minimal concern
- Some concern
- Major concern
- Critical concern
- No information

Overview of Animal Studies

- Study quality assessment
 - Follows <u>RoC Protocol</u>; details in <u>RoC Handbook</u>.
 - Consensus results of two independent reviewers reported in Appendix C of monograph.
- Initiation-promotion studies and transgenic studies; provided supportive information.
 - Dichloroacetic acid and trichloroacetic acid are complete carcinogens (Herren-Freund 1987), as well as cancer promoters (Pereira et al. 1997).
 - Dichloroacetic acid used as a positive to test TG.AC and p53 (+/-) transgenic mouse models, found to be inadequate models (NTP 2007b).
- Chronic carcinogenicity studies most informative.



Chronic Carcinogenicity Studies

Haloacetic acids	Species	Exposure route	Reference	Utility*
Monohaloacetic acids			*High = +++,	Moderate = ++, Low +
Monochloroacetic acid	Mouse ♂♀	Gavage	NTP 1992	+++
	Rat ∂°	Gavage	NTP 1992	++
	Rat 3	Drinking water	DeAngelo et al. 1997	+++
Dichloroacetic acids				
Dichloroacetic acid	Mouse ♂♀	Drinking water	Wood et al 2015	++
	Mouse ♂	Drinking water	DeAngelo <i>et al.</i> 1991, 1999	+++, ++
			Bull <i>et al.</i> 1990 Daniel <i>et al.</i> 1992	+
	Mouse ♀	Drinking water	Pereira <i>et al.</i> 1996	++
	Rat &	Drinking water	Richmond et al. 1995	++
			DeAngelo et al. 1996	++
	Mouse ♂♀	Drinking water	NTP 2007	
Dibromoacetic acid	Rat ∂♀	Drinking water Drinking water	NTP 2007	+++
	1 tat 0 +	Drinking water	1111 2007	
Bromochloroacetic acid	Mouse ♂♀	Drinking water	NTP 2009	+++
Dremeen decens deld	Rat ♂♀	Drinking water	NTP 2009	+++
Trichloroacetic acids				
Trichloroacetic acid	Mouse ♂	Drinking water	Herren-Freund et al. 1987	++
			Bull <i>et al.</i> 1990	+
	Mouse ♀	Drinking water	DeAngelo <i>et al.</i> 2008 Pereira <i>et al.</i> 1996	+++
	Mouse 32	Intraperitoneal Inj.	Von Tungeln <i>et al.</i> 2002	++
	Rat 3	Drinking water	DeAngelo et al. 1997	+++
Bromodichloroacetic acid	-	, and the second		
	Mouse ♂♀	Drinking water	NTP 2015	+++
	Rat ∂ ²	Drinking water	NTP 2015	+++



Haloacetic acids caused liver neoplasms

HALOACETIC ACID	R	AT	MOU	JSE
	Male	Female	Male	Female
Monochloroacetic acid	-	-	-	-
Dichloroacetic acid	HCC	NT	HCC	HCC
Trichloroacetic acid	-	NT	HCC	HCC
Dibromoacetic acid	-	-	HCC, HBI	HCC
Bromochloroacetic acid	-	-	HCC, HBI	HCC
Bromodichloroacetic acid	-	-	HCC, HBI	HCC, HBI

HCC = hepatocellular carcinoma; HBI = hepatoblastoma (carcinoma variant); NT = not tested; - = no liver tumors



HAAs induce hepatocellular carcinoma in male mice

A. Bromine-containing HAAs in male mice

90 80 70 90 60 77 *** 66 * 53 50 20 10

······ Trend (BCA)

50

0

Sources: NTP 2007a, 2009, 2015; DeAngelo et al., 1999, 2008

250

Dose mg/L

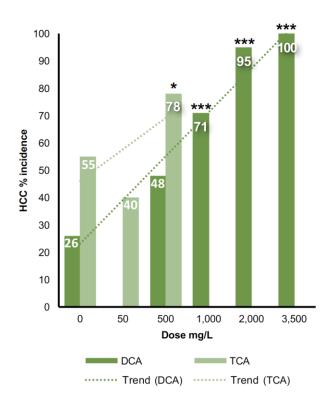
500

····· Trend (DBA)

····· Trend (BDCA)

1,000

B. Chlorine-containing HAAs in male mice





Other Cancer Sites

Drinking water exposure to brominated HAAs caused increased tumor incidence at sites in addition to liver

Haloacetic acid	Tissue site or neoplasia	Specie	es, sex
Dibromoacetic acid	Malignant mesothelioma	Rat	<i>3</i>
	Mononuclear cell leukemia	Rat	9
	Lung	Mouse	3
Bromochloroacetic	Malignant mesothelioma	Rat	3
acid	Mammary gland	Rat	9
	Large intestine	Rat	3 9
Bromodichloroacetic	Malignant mesothelioma	Rat	3
acid	Skin	Rat	3
	Mammary gland	Rat	9
	Harderian gland	Mouse	3



Other Cancer Sites

Drinking water exposure to brominated HAAs caused increased tumor incidence at sites in addition to liver

Haloacetic acid	Tissue site or neoplasia	Species, sex				
Dibromoacetic acid	Malignant mesothelioma	Rat	ð			
	Mononuclear cell leukemia	Rat	\$			
	Lung	Mouse	<i>3</i> *			
Bromochloroacetic	Malignant mesothelioma	Rat	3			
acid	Mammary gland	Rat	φ			
	Large intestine	Rat	3 9			
Bromodichloroacetic	Malignant mesothelioma	Rat	♂			
acid	Skin	Rat	3			
	Mammary gland	Rat	9			
	Harderian gland	Mouse	♂			



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	Mammary gland	Rat	9
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Drinking water exposure to haloacetic acids causes cancer in experimental animals*

		DC	Α		DBA				ВСА			TCA			BDCA					
Nacoleom or	Ra	ats	Mi	ice	Ra	ats	Mi	се	Ra	ıts	Mi	ce	Ra	ts	Mi	ce	Ra	ats	Mi	се
Neoplasm or tissue	М	F	М	F	М	F	М	F	М	F	М	F	М	F	М	F	М	F	М	F
Liver	Х		Х	Х			Х	Х			Х	Х			Х	Х			X	X
Mononuclear-cell leukemia						X														
Malignant mesothelioma					х				х								х			
Mammary gland										Х								х		
Lung							х													
Skin																	Х			
Harderian gland																			X	
Large intestine									Х	Х										

^{*}Monochloroacetic acid (MCA) exposure did not produce tumors in experimental animals.



Approach for Review

Defer vote on carcinogenicity in experimental animals

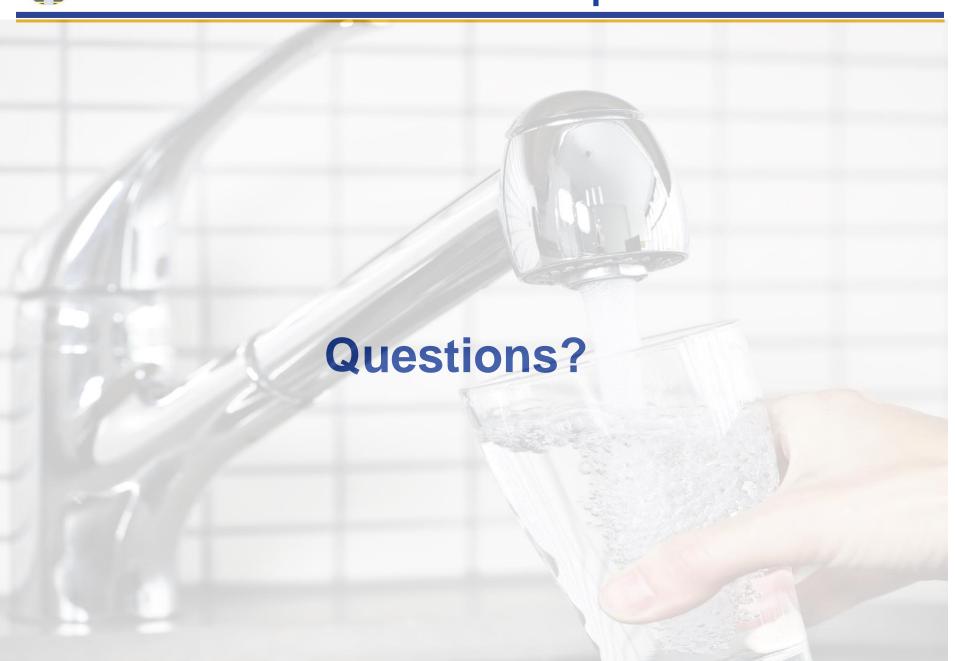
Evidence from studies of individual haloacetic acids in experimental animals

Mechanistic and other relevant data and evaluation of haloacetic acids as a class or subclass(es)

Vote on preliminary level of evidence conclusion and NTP listing recommendation for the haloacetic acids



Studies in Experimental Animals





Studies in Experimental Animals

Reviewer Questions

- Comment on whether the scientific information from cancer studies in experimental animals for each of the haloacetic acids found as water disinfection by-products is clear, technically correct, and objectively presented.
 - Identify any information that should be added or deleted.
- Comment on whether the approach and assessment of the utility of the animal carcinogenicity studies (study quality and sensitivity, ie, the ability to detect a true effect or hazard) for informing the cancer evaluation is systematic, transparent, objective, and clearly presented (Appendix C, Sections 4.2).
- Comment on and provide any scientific criticisms of NTP's cancer assessment of the experimental animal studies of exposure to the haloacetic acids found as water disinfection by-products and on how findings from the scientific evidence across studies were synthesized (Section 4.4).